STRESS, CLINICAL SYMPTOMS, AND PATIENT REPORT IN THE ASSESSMENT OF DISEASE ACTIVITY

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ACCREDITATION

This event has been approved as an accredited (Section I) group learning activity as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada (RCPSC). It has been produced under RCPSC guidelines for the development of co-developed educational activities between the Canadian Association of Gastroenterology (CAG) and AbbVie.

Canadian Association of Gastroenterology

L'Association Canadienne de Gastroentérologie

abbvie

Financial Interest Disclosure
(over the past 24 months)

No relevant financial relationships with any commercial interests

CANMEDS ROLES COVERED:

✓	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
✓	**Communicator** (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
✓	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
✓	**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
	Health Advocate (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
✓	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

OBJECTIVES

At the end of this session, participants will be able to:

- Recognize the role of patient experience and identify the utility of patient report approaches in the assessment of disease activity in patients with IBD.
- Identify the operating characteristics of serum and fecal inflammatory biomarkers for assessment of disease activity in patients with IBD.
- Determine the role of endoscopic and radiologic evaluation in the assessment of disease activity in patients with IBD.

IS THERE A ROLE FOR PATIENT INPUT?

- Patient is central in disease management
  - identify problem
  - flag exacerbations/flares
  - seek health care
  - self-manage
    - medication adherence

Image Public Domain Wikimedia Commons Branson 1992 Nat Cancer Institute

PATIENT REPORTED OUTCOMES

- PROs
  - = outcomes of treatment and disease management reported directly by patient
  - can include GI symptoms, pain, fatigue, mood, quality of life
  - can avoid outcome bias of physician, who is 'assessing own practice' El-Matary Can J Gastro 2014
- NIH developed PROMIS
  - PROs for chronic diseases; not disease specific; broad areas of functioning

PATIENT DISEASE MONITORING IN IBD

- 2006 FDA Recommendation
  - PROs - disease-specific symptoms as endpoints in clinical trials

- 2011 IBD Ahead Recommendation

Consistent use of standardized patient report tools for optimal disease monitoring

Papay JCC 2013

IBD clinical indices rely on patient report

STANDARDIZED PATIENT DISEASE MONITORING

NONINVASIVE CLINICAL INDICES FOR CD

Measure	Year	Information sources	Validated?
Crohn's Disease Activity Index	1976	Patient, physician, lab	Yes, partial
Harvey Bradshaw Index aka Simple Index or modified CDAI	1980	Patient, [physician]	r=.70/.80/.93 with CDAI
Van Hees Index aka Dutch Index	1980	Physician, lab	r=.57 with CDAI
Cape Town Index	1985	Patient, physician, lab	r=.76 with CDAI
short CDAI	2011	Patient	r=.89 with CDAI

Yoshida Can J Gastro 1999; Sandborn Gastro 2002; Vermeire 2010 Clin Gastro Hep; Thia IBD 2011; Peyrin_Biroulet Clin Gastro Hep 2015

COMMONLY USED IN CD:

	PROS	CONS
CDAI	Used 40 years; 'gold standard'; reasonably rigorous development; validated against physician assessment	No inflammation lab values; inter-rater reliability issues; modest correlation with endoscopy
HBI	Simple to use; single day; no labs; validated against CDAI; PPV .80 NPV .92 for cutoff 5	No inflammation lab values; modest correlation with endoscopy
sCDAI	Simple to use; 7 day symptoms; no lab/clinical assessment; validated against CDAI	No inflammation lab values; modest correlation with endoscopy

Sandborn Gastro 2002; Vermeire Clin Gastro Hep 2010; Loftus 2011; Thia Infl Bow Dis 2011

NONINVASIVE CLINICAL INDICES FOR UC

Measure	Year	Information sources	Validated?
Truelove Witts Severity Index	1955	Patient, physician, lab	no
partial Powell Tuck aka St. Mark's Index	1978	Patient, physician	Yes, partial
Clinical Activity Index aka Rachmilewitz Index	1988	Patient, assessor *physician or investigator*, lab	Yes, partial
Lichtiger Index aka modified Truelove Witts Severity Index	1990	Patient	Yes, partial
Activity Index (Seo Index)	1992	Patient, lab	Yes
Physician Global Assessment Investigators Global Assessment	1993 1998	Physician, patient Physician, patient	No No
Simple Clinical Colitis Activity Index	1998	Patient	Yes, partial
partial Mayo Score	2003	Patient, physician	Yes, partial
Patient-defined Remission	2005	Patient	Yes, partial
Manitoba IBD Index	2009	Patient	Yes, partial

D'Haens Gastro 2007; Hirai Dig Endo 2010; Walsh JCC 2014

- Most UC scales developed for clinical trials & not validated
- those easier to use implemented in more clinical trials

Validation/Reliability	Best performing noninvasive UC clinical disease indices
Discriminative validity	Partial Mayo, SCCAI
Construct validity	Partial Mayo, SCCAI, Rachmilewitz
Test-retest reliability	SCCAI, Rachmilewitz
Responsiveness to change	Partial Mayo, SCCAI

Turner Clin Gastro Hep 2009

- Best performing noninvasive clinical indices…
  - Are reasonably reliable and valid… to assess symptoms
  - Measure clinical symptoms/symptomatic disease activity
  - Rely on patient input

Is that enough?

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Is Endoscopy Necessary for the Measurement of Disease Activity in Ulcerative Colitis?

Peter D.R. Higgins, M.D., Ph.D., Marc Schwartz, M.D., John Mapili, M.D., and Ellen M. Zimmermann, M.D.
Division of Gastroenterology, University of Michigan, Ann Arbor, Michigan

CONCLUSIONS: Endoscopy items contribute little additional information to indices of disease activity in ulcerative colitis. The clinical practice of treating patients based on reported symptoms is appropriate. The use of noninvasive indices in clinical trials could lower study costs and may increase subjects' willingness to participate.

Clinical indices:
SCCAI and SEO; St. Mark's Index

Can Endoscopy Be Avoided in the Assessment of Ulcerative Colitis in Clinical Trials?

Ashwin D. Dhanda, MRCP,[*,†] *Tom J. Creed, MD,*[*] *Rosemary Greenwood, MSc,*[‡] *Bruce E. Sands, MD,*[§] *and Christopher S. Probert, MD*[*,†]

Conclusions: The Mayo score can be accurately predicted from the partial Mayo score. A noninvasive index can replace the Mayo score in future clinical trials.

(Inflamm Bowel Dis 2012;18:2056–2062)

Clinical Index: partial Mayo

- pMayo total score correlated .97 / .98 (week 4/8) with Mayo
- pMayo symptoms-only score correlated .89 and .90 with Mayo
- correctly classified severity (kappa .82; .92)

Physician Assessment of Ulcerative Colitis Activity Correlates Poorly with Endoscopic Disease Activity

Miguel Regueiro, MD, Joseph Rodemann, MD,* Kevin E. Kip, PhD†, Melissa Saul, MS,‡ Jason Swoger, MD,* Leonard Baidoo, MD,* Marc Schwartz, MD,* Arthur Barrie, MD, PhD,* and David Binion, MD**

Inflamm Bowel Dis 2011;17:1008-1014

- n=369 clinic visit & endoscopy
- Almost 1/2 with chronic inflammation not identified by physician assessment
- Poor agreement with endoscopy:
  sensitivity 56% specificity 81%
  NPV 56% PPV 81% kappa .35

WHAT IS 'DISEASE ACTIVITY' IN IBD?

- Symptoms? Inflammation? Elevated biomarkers? Abnormal histology?

- Treatment goals: decrease symptoms

↓

control inflammation

↓

achieve mucosal healing

Bouguen Clin Gastro Hep 2015

WHAT DO SYMPTOMS TELL US?

Symptoms may flag underlying pathology, but…

Symptoms can occur in the absence of inflammation

Berrill Alim Pharm 2013

Inflammation can occur in the absence of symptoms

Baars Inflamm Bowel Dis 2012

SYMPTOMS: MORE THAN INFLAMMATION

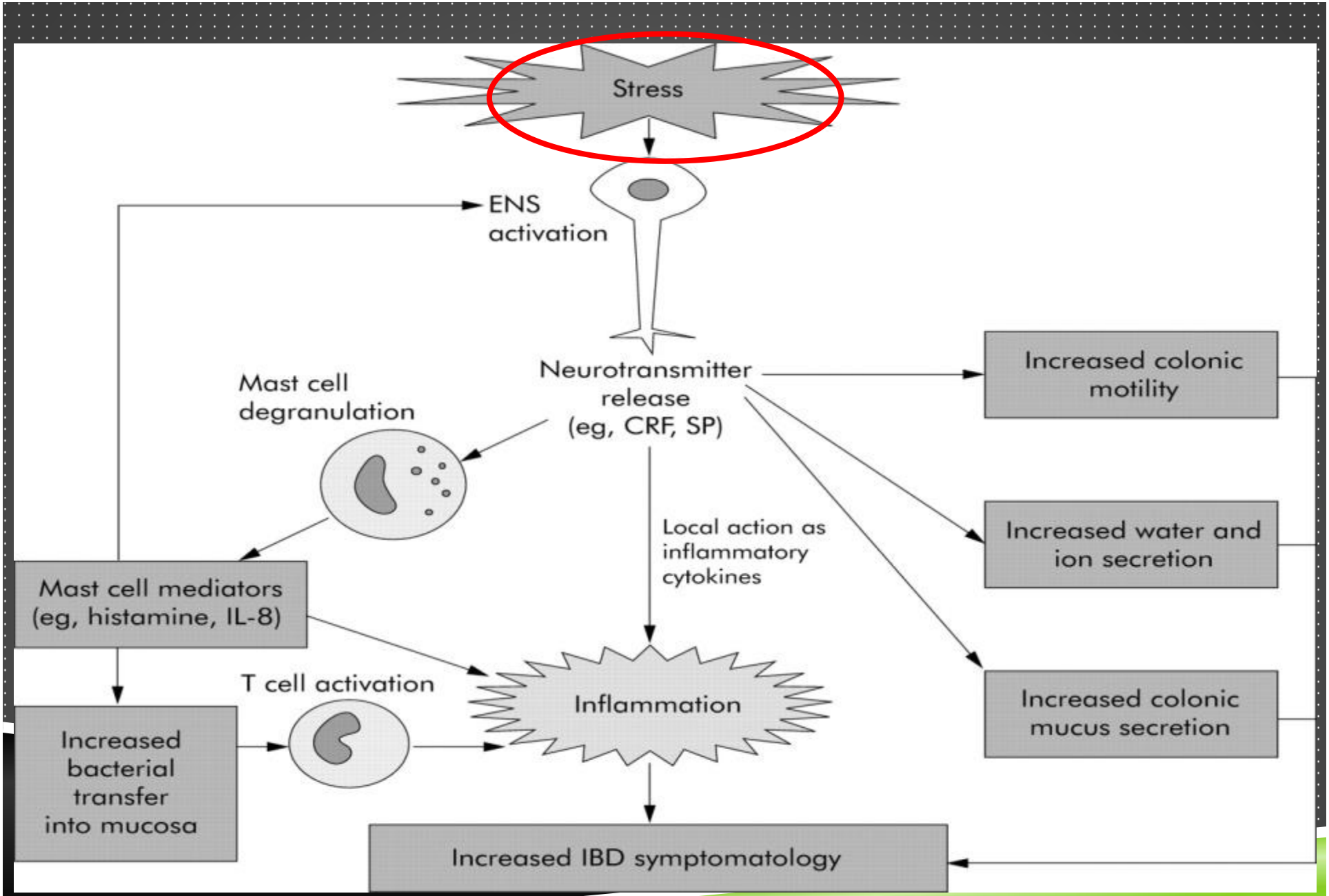
- SONIC trials: 18% with high CDAI (>220) no endoscopic evidence of active CD/inflammation[1]
- CDAI scores: IBS > IBD; CDAI did not differentiate samples[2]
- CD symptoms (HBI/MIBDI) not associated with elevated FCAL[3]
  UC symptoms (PTI/MIBDI) modestly associated with FCAL[3]

[1]Columbel NEJM 2010; [2]Lahiff APT 2013 [3]Targownik AJG 2015

SYMPTOMS AND STRESS

- CD and UC symptoms significantly associated with stress (and not/minimal with FCAL)[1] n=478
- stress predictive of symptomatic disease activity in subsequent 3 month period[2] n=600
- stress predictive of more frequent IBD symptoms over subsequent 5 years[3] n= 337

[1]Targownik AJG 2015; [2]Bernstein AJG 2010; [3]Sexton DDW 2013



Mawdsley & Rampton Gut 2005;54:1481-1491
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THROW OUT THE BABY…?

40 year history of CDAI; keep symptom subset

Symptoms necessary but not sufficient

Buguen Clin Gastro Hep 2015

Both symptoms & inflammation guide treatment decision

Image Graff July 1990

BUILDING BETTER SYMPTOM INDICES

Mt Sinai group Zittan DDW 2015

Improve concordance of clinical index and endoscopic scores?

CD n=88	**Concordance with endoscopic disease**
HBI + PRO (do you think disease active?)	Did not improve
HBI + PRO + DR-RO (do you think patient disease inactive to severe?)	Significantly improved
HBI + PRO + DR-RO + CRP	Significantly improved

BUILDING BETTER SYMPTOM INDICES

Manitoba group Sexton DDW 2014

Identify range of clinically relevant symptoms?

CD and UC n=234	**Symptoms of IBD Inventory* 12 items**
HBI & PTI self report (validated against clinician administered HBI/PTI	r=.66 HBI; r=.72 PTI
Global physician assessment (inactive to severe)	r=.63

*Symptoms included fatigue, number daily bowel movements, number liquid bowel movements, urgency, abdominal pain, bloating, waking due to pain

BUILDING BETTER SYMPTOM INDICES

Oxford Clinical Trials group Jairath APT 2015

Minimal symptoms needed?

- 2 UC cohorts: n=194 and n=181
- Patient symptoms from Mayo Clinic Score
  - Rectal bleeding; stool frequency
- 2 item PRO differentiated between active drug and placebo

AN APP FOR THAT: PATIENT ONLINE MONITORING

- Mobile app Health index for IBD[1]
  - CD: liquid stool frequency, abdominal pain, patient well being, 'disease control'
  - UC: stool frequency, abdominal pain, rectal bleeding, patient assessed disease control
  - ROC .90 CD .91 UC for clinical indices; ROC .63 CD, .82 UC for endoscopic activity
  - Responsive to disease activity changes
- Online SCCAI[2]
  - Compared to physician-assessed SCCAI in clinic, blinded, assessed within 48 hours
  - r=.79; 85% agreement for remission or activity NPV for active disease 94% PPV 68%

[1]van Deen Clin Gastro Hep 2015
[2]Marin-Jimenez AJG 2016

Image creative commons wikimedia; 'mobile devices' Hlundgaard 2010

- Current noninvasive indices
  - Standardize use
  - Standardize cutoff scores

- Develop new noninvasive indices
  - Include symptom subset from current indices
  - Identify meaningful symptoms for CD and UC; individualized symptom profile?

- Use standardized patient information in combination with biomarker; validate using endoscopic data

Bouguen Clin Gastro Hep 2015; Levesque Gastro 2015; Peyrin-Biroulet Clin Gastro Hep 2015

Image Creative commons; 'Confusion' B. Metcalfe 2012

biomarkers

endoscopy/imaging

Ed Loftus

Talat Bessissow

Image Creative commons; Arm wrestlIng P. Dansten March 2015

SYMPTOMS + BIOMARKERS; ENDOSCOPY

Graff, Loftus, Bessissow

Creative Commons My fingers by Zita 952 Dec 2012

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www.ibdmanitoba.org

Photo IBD team June 2009 Winnipeg MB

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